PCT/IB03/4439 #3

सत्यमेव जयते

INTELLECTUAL PROPERTY **INDIA**

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.1024/Del/2002 dated* ***8th October 2002.***

Witness my hand this 22nd day of December2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

1224-02

- 8 OCT 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **" PROCESS FOR THE PREPARATION OF (Z)– ISOMER ENRICHED 7-AMINO-3-PROPEN-1-YL-3-CEPHEM-4-CARBOXYLIC ACID"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR
b. NEERA TEWARI
c. SHAILENDRA KUMAR SINGH
d. BISHWA PRAKASH RAI

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, YATENDRA KUMAR, NEERA TEWARI, SHAILENDRA KUMAR SINGH, BISHWA PRAKASH RAI of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(YATENDRA KUMAR)

b. Neera Tewari

(NEERA TEWARI)

c. Shailendra Kumar Singh

(SHAILENDRA KUMAR SINGH)

d. BPRai

(BISHWA PRAKASH RAI)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **684791** dated **01.10.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **8TH** day of **OCTOBER, 2002.**

For Ranbaxy Laboratories Limited

Sean

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

- 8 OCT 2002

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

DUPLICATE

PROCESS FOR THE PREPARATION OF (Z)– ISOMER ENRICHED 7-AMINO-3-PROPEN-1-YL-3-CEPHEM-4-CARBOXYLIC ACID

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

(A Company incorporated under the Companies Act, 1956)

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The invention relates to a process for enrichment of the (Z)-isomer amount in a mixture of the (Z)- and (E)- isomers of 7-amino-3-(1-propen-1-yl)-3-cephem-4-carboxylic acid of formula I, as shown in the accompanied drawings.

The compound of formula I is an important intermediate for the preparation of 3-propenyl cephalosporin antibiotics such as cefprozil and BAYv 3522. Synthetic processes for the production of these antibiotics generally yield mixtures containing both the (Z)- and (E)-isomers. The Z-configuration of the propenyl group is related to the activity of 3-propenyl cephalosporin antibiotics against the gram negative bacteria, hence, the need to minimize the undesired (E) - isomer in these antibiotics.

US Patent No. 4,727070 describes a process for preparing cefprozil, substantially free of the corresponding E-isomer, which involves preparation of sodium salt of imidazolidinone derivative of a mixture containing cefprozil and its corresponding E-isomer, and separation of the imidazolidinone derivative isomers, based on their differential solubility.

US 6,136,967 describes a process for preparing (Z)-isomer enriched 7-amino-3-(1-propen-1-yl)-3-cephem-4-carboxylic acid of formula I involving depleting the corresponding (E)-isomer in a mixture of the (Z)- and (E)- isomers of carboxylic acid of formula I, which comprises subjecting a solution of the mixture to adsorption chromatography.

US 5,869,648 describes a process for preparing a (Z)-isomer enriched carboxylic acid of formula I, which comprises reacting a mixture of (Z) and (E)- isomers with a lithium, sodium or potassium base, ammonia or an amine to form a mixture of the (Z) and (E)-isomers of the corresponding salts, and depleting the (E) isomer salt from (Z)- isomer salt in a solvent or solvent mixture in which the two isomers have different solubility, to recover the enriched (Z)- isomer salt of carboxylic acid of formula I, and converting it to the free acid.

US 6333049 gives another variant of the above process based on the differential solubility of the (Z) and (E)- isomers of the hydrochloride salt of the carboxylic acid of formula I.

Cephalosporanic acid derivatives with a (cyclo)alkylideneammonio group are provided in US 5359058, and are used as a method of protecting an amino group in synthesis wherein amino carboxylic acids have to be protected. Cephalosporanic acid derivatives with an aldimine substituent at the 7-position have been described for instance by W. A. Spitzer, T. Goodson, R. J. Smithey and I. G. Wright, J.C. Soc. Chem. Comm., 1338 (1972).

Such compounds were therefore useful as synthetic intermediates. However, there has been no application of such derivatives to the separation of mixtures of cephalosporins where geometric isomerism about a double bond exists.

The present invention provides a process for the preparation of (Z)- isomer enriched 7-amino-3-(1-propen-1-yl)-3-cephem-4-carboxylic acid of formula I, as shown in the accompanied drawings, which comprises:

(i) reacting a mixture of the (Z)- and (E)- isomers of carboxylic acid of formula I with a compound of formula II, as shown in the accompanied drawings, wherein R_1 and R_2 are independently hydrogen, alkyl, alicyclic, aryl, aralkyl, or R_1 and R_2 together form a 5 to 7 membered carbocyclic ring; in the presence of an acid, HX to form an alkylidene ammonio salt derivative of formula III, as shown in the accompanied drawings, wherein R_1 and R_2 are the same as above and X^- is an anion from the acid HX,

(ii) obtaining (Z)-isomer enriched alkylidene ammonio salt of formula III from the above reaction mixture, and

(iii) converting it to 7-amino-3-(1-propen-1-yl)-3-cephem-4-carboxylic acid of formula I, which is obtained as the free acid or in salt form.

The free acid or a salt of the mixture of the (Z)- and (E)- isomers of compound of formula I may be used as the starting compound in the reaction and may have up to 30% of the (E)- isomer.

Alkyl group may be C_{1-6} straight or branched chain alkyl. Alicyclic group may be a 5 to 7 membered carbocyclic group. Aryl group may be phenyl, which may be further substituted by alkyl, halogen, alkoxy or hydroxy groups.

The compound of formula II may be a ketone such as acetone, methyl isobutyl ketone, cyclohexanone, cyclopentanone, or benzophenone; or an aldehyde such as benzaldehyde, acetaldehyde or formaldehyde.

The acid may be any suitable inorganic or organic acid. The acid is typically added as a concentrated anhydrous solution or purged into the reaction mixture in the gaseous form. Suitable inorganic acids include hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid and perchloric acid. Suitable organic acids include formic acid and acetic acid.

Thus, X^- in the salt derivative of formula III may be Cl^-, Br^-, I^-, ClO_4^-, $H_2SO_4^-$, $HCOO^-$ or $CH_3\ COO^-$.

The acid and the aldehyde / ketone of formula II used in the reaction may also act as solvents for the reaction. In addition, a suitable organic solvent may also be employed. Where the aldehyde / ketone used is not suitable solvent material, the aldehyde/ketone may be provided as a solute in an organic solvent. The solvent may be any reaction inert non aqueous organic solvent or solvent mixture in which the (Z)- and (E)-isomers of alkylidene ammonio salt derivative of formula III have different solubilities.

A solvent is selected in which the (Z)- isomer of the salt derivative of formula III is relatively insoluble, while the (E)-isomer is soluble. Testing of various combinations of aldehydes/ketones, acids, and solvents to accomplish this purpose is within the skill of the laboratory chemist.

Operating in a practically water-free system, the mixture of the (Z)- and (E)- isomers of carboxylic acid of formula I is dissolved / suspended in an acid, and then a compound of formula II and optionally an organic solvent is/are then added. Once the salt derivative of formula III is formed, the reaction mixture is optionally diluted with a counter solvent or a mixture of counter solvents, whereby the crystalline (Z)- isomer

enriched derivative of formula III is crystallized out. Selective precipitation of the (Z)-isomer of the salt derivative of formula III occurs due to the lower solubility thereof, relative to the (E)-isomer derivative. The crystalline (Z)- isomer enriched derivative of formula III is recovered by filtration or centrifugation.

Examples of organic solvents are carboxylic acids, e.g. acetic acid, amides, e.g. dimethylformamide; sulfoxide, e.g. dimethylsulfoxide; sulfone, e.g. sulfolane; halogenated hydrocarbons, e.g. dichloromethane; ketones, e.g. acetone; esters, e.g. ethyl acetate; ethers, e.g. tetrahydrofuran; nitriles e.g. acetonitrile or mixtures of these solvents. Further solvents may be added in admixture such as diethyl ether or tert. butyl methyl ether.

Suitable organic counter solvents are in particular ketones, e.g. acetone; ethers, e.g. tert.butyl methyl ether, diethylether, tetrahydrofuran; esters, e.g. ethyl acetate, isopropyl acetate; nitriles, e.g. acetonitrile; or mixtures thereof.

The reaction may be performed at room temperature or at a somewhat elevated temperature, such as a temperature of about 20 to 55° C, or at a temperature of about 0 to 45° C. The product of formula III is crystallized out at room temperature or at a lower temperature, such as a temperature of about 0 to 30° C, or at a temperature of about 0 to 15°C.

According to another variant, the derivative of formula III obtained from the reaction may be suspended or dissolved in a solvent or solvent mixture in which the (E)-isomer of formula III is better soluble than the corresponding (Z)-isomer. Suitable solvents are organic solvents mentioned above. Precipitation is then induced by e.g. adjustment of the solubility product of the (Z)- or (E)-isomer optionally by addition of one of the above mentioned counter solvents, whereby the derivative of formula III, with a reduced (E)-amount is obtained.

The derivative of formula III, which is thereby much improved in its Z/E ratio may subsequently be converted again into the carboxylic acid of formula I in conventional manner, e.g. by means of pH adjustment in water to the approximate isoelectric point.

Compounds of formula I containing various amounts of Z/E isomers, from a ratio of 91:9 to 99:1 or more may be prepared in good yields and purity, as described by the processes herein. The process may be repeated in order to obtain the desired Z/E ratio.

The crystalline alkylidene ammonio salt derivatives of formula III are new and also form part of the invention. The derivatives of formula III having a Z/E ratio of at least 91:9 or more are also new and form part of the invention. These compounds are useful as intermediates in the process for the preparation of (Z)-isomer enriched 7-amino-3-(1-propen-1-yl)-3-cephem-4-carboxylic acid of formula I.

The (Z)-isomer enriched carboxylic acid of formula I is converted to a 3-propenyl cephalosporin antibiotic by methods known in the art, such as those described in US 4699979, US 5171854, US 5608055, US 2002/120136 and US 6060268, which are incorporated herein by reference.

In particular, cefprozil may be prepared by a process comprising:

i) producing a mixed carboxylic acid anhydride by reacting a Dane salt with ethyl chloroformate, and

ii) reacting the obtained mixed carboxylic acid anhydride with a silylated (Z)-isomer enriched 7-amino-ceph-3-em-4-carboxylic acid of formula I obtained by the process of the present invention, to obtain cefprozil in good yield and purity.

Dane salt may be selected from sodium or potassium (D)-N-(1-methoxycarbonyl-propen-2-yl)-α-amino-p-hydroxyphenylacetate and sodium or potassium (D)-N-(1-ethoxycarbonylpropen-2-yl)-α-amino-p-hydroxyphenylacetate.

A base, e.g. a tertiary amine base such as N-methyl morpholine, N,N-dimethyl benzyl amine, triethylamine, pyridine, picoline, or lutidine is used as a catalyst for mixed carboxylic acid anhydride formation.

The mixed anhydride may be prepared in a solvent conventionally used such as a halogenated hydrocarbon, e.g. methylene chloride ; a ketone e.g. methyl isobutyl ketone; an ester e.g. ethyl acetate; or an aromatic hydrocarbon e.g. toluene; and a co-solvent such as an organic amide. Organic amide is selected from formamide, acetamide, N,N-dimethyl formamide, N-methylacetamide, N,N-dimethylacetamide and N-methylpyrrolidone.

The solvents used for mixed anhydride preparation may also be used for step ii) condensation.

Cefprozil containing various amounts of Z/E isomers, from a ratio of 91:9 to 99:1 or more may be prepared, as described by the processes herein.

In the following section preferred embodiments are described by way of examples to illustrate the process of the invention. However, these are not intended in any way to limit the scope of the present invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.

Preparation of (6R,7R)-7-isopropylideneammonio-3-[(Z/E)-1-propen-1-yl]-3-cephem-4-carboxylic acid hydrochloride

EXAMPLE – 1

Hydrogen Chloride gas (100 g) was passed through a mixture of acetic acid (200 ml) and acetone (500 ml) at 25 to 35°C. 7-Amino-3-(1-propen-1-yl)-3-cephem-4-carboxylic acid (100 g, Z/E ratio : 75/25) was added at 30 – 35°C in 2 to 3 minutes and stirred to obtain a clear solution. Acetone (500 ml) was then added in 5 minutes and the stirring continued. Solid separated from the clear solution. The reaction mixture was cooled to 0 to 5°C and stirred for 2 to 3 hours. The solid was filtered and washed with acetone and dried to get 100 g of the title compound.

Z/E Ratio :90.0 / 9.5, (E)- isomer content (By NMR) : 9.0%, Chloride content : 12%

^{1}HNMR (300 MHz) : (CF_3COOD) δ value

2.54 (d, 3H, CH_3, Z-Isomer), 2.56 (d, 3H, CH_3, E-Isomer)

3.51 (S, 3H, $\underline{H_3C}$ / H_3C >C = N—), 3.51 (S, 3H, H_3C / $\underline{H_3C}$ >C = N—)

4.25 - 4.55, (m , 2H, —S$C\underline{H_2}$—), 6.3 (d, 1H, β-lactam),

6.73 - 6.86 (m, 2H, CH = C$\underline{H}CH_3$ & β-lactam),

7.22 - 7.34 (d, 1H, C$\underline{H}$ = $CHCH_3$ & Z-isomer & E-Isomer)

IR (KBr, cm^{-1}) : 3426, 2906, 1780, 1707, 1653, 1621, 1404,1351, 1213, 809, 718 and 691

EXAMPLE – 2

7-Amino-3-(1-propen-1-yl)-3-cephem-4-carboxylic acid (100 g, Z/E : 80/20) was dissolved in a mixture of acetic acid (200 ml) and acetone (500 ml) saturated with hydrogen chloride gas at 30 – 35°C. After 5 min., acetone (500 ml) was added and a solid separated from the clear solution. After stirring at 0 to 5°C for 2 to 3 hours the title product was filtered, washed with acetone and dried.

Yield	:	110 g
Z/E Ratio	:	91.0 / 9.0
(E)- isomer content (By NMR)	:	8.5%
Chloride content	:	14%

The following table demonstrates the experiments carried out with variable Z/E ratio of carboxylic acid of formula I w.r.t. yield and Z/E ratio of the isopropylidene ammonio derivative of formula III obtained.

Table – I

Example No.	Input (formula I)	Input Z/E Ratio	Yield (w/w) of derivative of formula III	Achieved Z/E
3	100 g	80 / 20	110 g	92.0 / 8.0
4	100 g	85 / 15	100 g	92.0 / 8.0
5	100 g	88.5 / 11.5	115 g	93.5 / 6.5

Regeneration of 7-amino-3-[(Z/E)-1-propen-1-yl]-3-cephem-4-carboxylic acid from 7-isopropylideneammonio-3-[(Z/E)-1-propen-1-yl]-3-cephem- 4-carboxylic acid hydrochloride

EXAMPLE – 6

7-Isopropylideneammonio-3-[(Z/E)-1-propen-1-yl]-3-cephem-4-carboxylic acid hydrochloride salt (from example-I, 100 g Z / E : 90.0 / 9.5) was suspended in water (2000 ml) and pH was adjusted to 8.0 – 8.5 to obtain a clear solution. Activated carbon was added and stirred for 15 minutes, filtered and washed with water. The pH of the filtrate was adjusted to 3.0 – 3.5 with 6N hydrochloric acid. Solid so obtained was stirred for additional 30 minutes at room temperature and then filtered, washed with water followed by acetone. Drying at 48 to 50°C resulted in 75 g of the title product.

Z/E Ratio: 91.0 / 9.0, E-Content (By NMR) : 8.9%, Assay : 99.5%(By HPLC)

NMR (300 MHz, CF_3COOD) : 2.47 – 2.50 (d, 3H, $\underline{CH_3}$, Z-isomer), 2.66 – 2.68 (d, 3H, $\underline{CH_3}$, E-isomer), 4.17 – 4.43 (m, 2H, $S\underline{CH_2}$), 5.92 – 6.1 (m, 2H, b-lactam), 6.71 (dq, 1$\underline{H}$, -CH = C$\underline{H}$-CH_3), Z-isomer), 7.21 – 7.24 (d, 1H, $\underline{CH}$ = CH-CH_3), Z-isomer)

EXAMPLE – 7

7-Isopropylideneammonia-3-[(Z/E)-1-propen-1-yl]-3-cephem -4-carboxylic acid hydrochloride salt (100 g, Z/E : 92.0 / 8.0) from Example – 3 (Table – I) was suspended in water(2500 ml) and dissolved by adjusting pH to 8.0 to 8.5 at room temperature. The reaction mixture was filtered and pH adjusted to 3.0 – 3.5 with 6N hydrochloric acid to obtain the product.

Yield	:	78 g
Z/E Ratio	:	92.0 / 8.0
(E)- isomer content (By NMR)	:	7.8%
Assay (By HPLC)	:	99.7%

Preparation of 7[(D)-2-amino-2-(4-hydroxyphenyl) acetamido]-3-(Z/E)-1-propenyl]-ceph-3-em-4-carboxylic acid (cefprozil) dimethylformamide solvate

EXAMPLE – 8

Solution A - To a stirred slurry of 7 amino-3-[(Z/E)-1-propen-1-yl]-cephe-3-em-4-carboxylic acid (50 g, Z/E : 92.0 / 8.0) in methylene chloride (300ml) were added hexamethyldisilazane (25.2g), trimethylchlorosilane (17.6g) and imidazole(0.5g). Reaction mixture was refluxed for 3.5 to 4 hours and then cooled to -10 to -15°C.

Solution B - Potassium (D)-N-[1-methoxycarbonyl propen-2-yl]- α-amino-p-hydroxyphenylacetate (dane salt, 70.75g) was stirred in methylene chloride (300ml). Slurry was cooled to -25°C and N,N - dimethylformamide (DMF, 400ml) was added. Slurry was cooled to -30 to - 35°C and N-methyl morpholine(0.46g) was added, followed by addition of ethylchloroformate(8.2g) at -35°C. Stirred for 1.0 hour and cooled to -45°C.

Added above silylated mass (solution A) into mixed anhydride (solution B) at -45°C and stirred for 2.0 - 3 hours at -25 to -20°C. Reaction was monitored by HPLC. After completion of reaction a mixture of water and hydrochloric acid was added to the reaction mixture and stirred for 10 minutes. Aqueous layer was separated.

Dimethylformamide (500ml) was added to the aqueous layer followed by activated carbon (5g). Stirred for 5 minutes, filtered the aqueous layer and washed with dimethylformamide. pH of aqueous phase was adjusted to 6.5 with ammonia solution at 25-30°C. White solid obtained was filtered and washed with dimethylformamide followed by acetone. After drying at room temperature under vacuum 98g (yield : 92%, Z/E : 92.0 / 8.0) of cefprozil was obtained as dimethyl formamide solvate.

WE CLAIM:

1. A process for the preparation of (Z)- isomer-enriched 7-amino-3-(1-propen-1-yl)-3-cephem-4-carboxylic acid of formula I, as shown in the accompanied drawings, which comprises:

   (i) reacting a mixture of the (Z)- and (E)- isomers of carboxylic acid of formula I with a compound of formula II, as shown in the accompanied drawings, wherein R_1 and R_2 are independently hydrogen, alkyl, alicyclic, aryl, aralkyl, or R_1 and R_2 together form a 5 to 7 membered carbocyclic ring; in the presence of an acid, HX to form an alkylidene ammonio salt derivative of formula III, as shown in the accompanied drawings, wherein R_1 and R_2 are the same as above and X^- is an anion from the acid HX,

   (ii) obtaining (Z)-isomer enriched alkylidene ammonio salt derivative of formula III from the above reaction mixture, and — redundant plurality

   (iii) converting it to 7-amino-3-(1-propen-1-yl)-3-cephem-4-carboxylic acid of formula I, which is obtained as the free acid or in salt forms.

2. The process according to claim 1, wherein the compound of formula II is a ketone.

3. The process according to claim 2, wherein the ketone is selected from the group consisting of acetone, methyl isobutyl ketone, cyclohexanone, cyclopentanone, and benzophenone.

4. The process according to claim 1, wherein the compound of formula II is an aldehyde.

5. The process according to claim 4, wherein the aldehyde is selected from the group consisting of benzaldehyde, acetaldehyde and formaldehyde.

6. The process according to claim 1, wherein the acid is an inorganic acid.

7. The process according to claim 6, wherein the inorganic acid is selected from the group consisting of hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid and perchloric acid.

8. The process according to claim 1, wherein the acid is an organic acid.

9. The process according to claim 1, wherein the organic acid is selected from formic acid and acetic acid.

10. The process according to claim 1, wherein the reaction is performed in an inert non aqueous organic solvent or solvent mixture in which the (Z)- and (E)-isomers of derivative of formula III have different solubilities.

11. The process according to claim 10, wherein the solvent is one in which the (Z)-isomer of the salt derivative of formula III is relatively insoluble, while the (E)-isomer is soluble.

12. The process according to claim 10, wherein the organic solvent is selected from carboxylic acids, amides, sulfoxides, sulfones, halogenated hydrocarbons, ketones, esters, ethers, nitriles or mixtures thereof.

13. The process according to claim 11, wherein the solvent is selected from acetic acid, dimethylformamide, dimethylsulfoxide, sulfolane, dichloromethane, acetone, ethyl acetate, tetrahydrofuran, acetonitrile or mixtures thereof.

14. The process according to claim 1, wherein the reaction mixture is diluted with a counter solvent or a mixture of counter solvents, to obtain the (Z)- isomer enriched derivative of formula III.

15. The process according to claim 1, wherein the organic counter solvent is selected from ketones, ethers, esters, nitriles, or mixtures thereof.

16. The process according to claim 15, wherein the organic counter solvent is selected from acetone, tert.butyl methyl ether, diethylether, tetrahydrofuran, ethyl acetate, isopropyl acetate, acetonitrile, or mixtures thereof.

17. The process according to claim 1, wherein the reaction is performed at a temperature of about 20 to 55° C.

18. The process according to claim 17, wherein the reaction is performed at a temperature of about 30 to 45° C.

19. The process according to claim 1, wherein the derivative of formula III is crystallized out at a temperature of about 0 to 30°C

20. The process according to claim 1, wherein the derivative of formula III is crystallized out at a temperature of about 0 to 15°C.

21. The process according to claim 1, wherein carboxylic acid of formula I containing Z/E isomers, from a ratio of 91:9 to 99:1 is obtained.

22. The process according to claim 1, wherein the (Z)-isomer enriched carboxylic acid of formula I is converted to a 3-propenyl cephalosporin antibiotic.

23. The process according to claim 1, wherein the (Z)-isomer enriched carboxylic acid of formula I is converted to cefprozil.

24. The process according to claim 23, wherein cefprozil containing Z/E isomers from a ratio of 91:9 to 99:1 is prepared.

23. The process according to claim 1, wherein the (Z)-isomer enriched 7-amino-3-(1-propen-1-yl)-3-cephem-4-carboxylic acid of formula I is silylated, and reacted with a

mixed carboxylic acid anhydride produced by reacting a Dane salt with ethyl chloroformate, to obtain cefprozil.

24. The process for the preparation of (Z)-isomer enriched 7-amino-3-(1-propen-1-yl)-3-cephem-4-carboxylic acid of formula I, as herein described and illustrated by the examples herein.

Dated this 8TH day of **October , 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

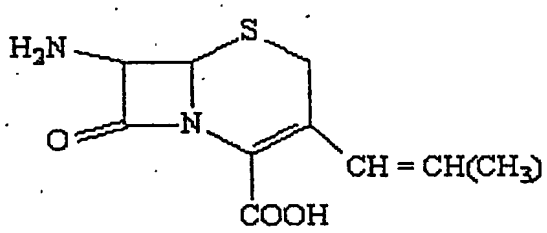
Ranbaxy Laboratories Limited

Application No.

No. of sheets = 01

Sheet 01 of 03

- 8 OCT 2002

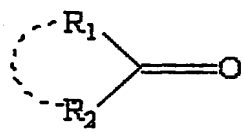


FORMULA I

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

- 8 OCT 2002



FORMULA II

DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

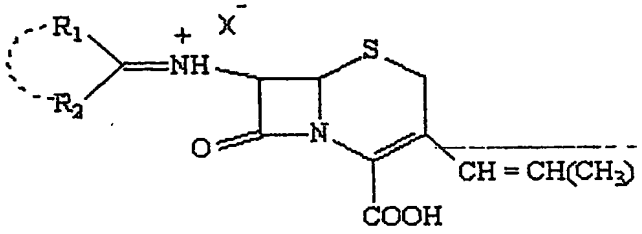
Ranbaxy Laboratories Limited

Application No.

No. of sheets = 01

Sheet 03 of 03

- 8 OCT 2002



FORMULA III

DUPLICATE

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

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